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TERRY

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EXAMINER

HM22/0705

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 15

Application Number: 09/365, 349
Filing Date: 07/30/99
Appellant(s): Terry et al.

Richard Aaron Osman
For Appellant

EXAMINER'S ANSWER

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This is in response to appellant's Supplemental Brief on appeal filed January 25, 2001.

(1) *Real Party in Interest*

The statement contained in the brief is taken to be true as stated by Appellant.

(2) *Related Appeals and Interferences*

The statement contained in the brief is taken to be true as stated by Appellant.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

Claims 1-3, 5-8, 13-15, 19-20, 22 stand on appeal.

Claims 4, 9-12, 16-18, 21, 23-24 were inadvertently included in the enablement rejection of 10/24/01. The claims now stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is substantially correct. The appellant's discourteous statements on page 2 of the Brief of 25 January 2001 regarding the proposed Examiner's amendment of 09/19/00 are noted. However, the mission of the USPTO is to help Applicants/Appellants get valid patents, and the Examiner has properly carried out the mission. Appellants' arguments in the first Appeal Brief of 8/8/00 that Arisi et al's transgenic poplars overexpressing the gamma-glutamylcysteine

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synthetase (ECS) could not accumulate Cd; and in the Supplemental response of 09/21/01, regarding the unpredictability in the transformation of plants to overexpress ECS for an enhanced heavy metal accumulation/tolerance as evidenced by Arisi et al's or Noctor et al's transformed poplars or Goldsbrough's transformed Arabidopsis; and the limited working examples in Appellants' disclosure; led the Office to withdraw the art rejections previously of record, and to institute the new ground of rejection under 35 USC 112, first paragraph, set forth in the Official action of 10/24/2000 and which is repeated here below. The proposed Examiner's Amendment of 19 September 2000 was offered in good faith in an effort to expedite prosecution and accelerate the prompt issuance of a valid patent. Regrettably, this course of action was not chosen by Appellant.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Whether claims 1-3, 5-8, 13-15, 19-20, and 22 were properly rejected under 35 U.S.C., first paragraph (scope of enablement). Claims 4, 9-12, 16-18, 21, 23-24 were inadvertently included in the rejections of 10/24/2000. The rejection to claims 1-24 under 112, first paragraph (Written Description rejection) has been withdrawn, in view of Appellants' arguments in the Supplemental Brief of 1/25/01.

(7) *Grouping of Claims*

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The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because claims 1-3, 5-8, 13-15, 19-20, 22 are not separately patentable and are subject to the same rejection set forth below.

(8) *Claims Appealed*

A correct copy of appealed claims appears on pages 18-21 of the Appendix to the appellant's brief.

(9) *Prior Art of Record*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

De Knecht et al. "Evidence against a role for Phytochelatins in Naturally Selected Increased Cadmium Tolerance in *Silene vulgaris* (Moench) Garcke." New Phytol., Vol. 122, (1992) , pp. 681-688, especially pages 685-687.

Delhaize et al. "Poly(gamma-glytamylcysteinyl)-glycine Synthesis in *Datura innoxia* and Binding with Cadmium: Role in Cadmium Tolerance. Plant Physiology, Vol. 89 (1989), pp. 700-706, especially page 702, 2nd full paragraph of the Results.

Noctor et al. "Glutathione: Biosynthesis, Metabolism and Relationship to Tolerance Explored in Transformed Plants". Journal of Experimental

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Botany, Vol. 49, No. 321 (April 1998), pp. 623-647, especially page 640, column 1, bottom paragraph.

Peter Goldsbrough. "Metal Tolerance in Plants: The Role of Phytochelatins and Metallothioneins". Ann Arbor Press (1999), pp. 221-228, especially page 230, last full paragraph.

Chen et al. "Increased Activity of Gamma-Glutamylcysteine Synthetase in Tomato Cells Selected for Cadmium Tolerance." Plant Physiology. Vol. 106 (1994), pp. 233-239, especially page 238, column 2, last full paragraphs.

Arisi et al. "Modification of Thiol Contents in Poplars (*Populus tremula* X *P. alba*) Overexpressing Enzymes Involved in Glutathione Synthesis." Planta. Vol. 203 (1997), pp. 362-372, especially page 363, Materials and Methods.

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(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-3, 5-8, 13-15, 19-20, 22 on appeal are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transformed *Brassica juncea* overexpressing a glutamylcysteine synthetase (ECS) for an improved tolerance to selected heavy metals, does not reasonably provide enablement for any transformed plant capable of enhancing accumulation of a wide variety of heavy metals by overexpressing an ECS, and a method for decreasing heavy metal content of a medium by growing said plant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to any plant which is genetically engineered to overexpress glutamylcysteine synthetase for an enhanced heavy metal accumulation, said plant having at least 50% enhanced accumulation of heavy metals, including cadmium, mercury, uranium, chromium, molybdenum, and tungsten, as compared to a corresponding wild type plant, a method for decreasing heavy metal content of any medium by growing said transformed plants, wherein the plant grows not significantly differently than the corresponding wild type plant under non-heavy metal conditions. In contrast, the specification provides guidance only for the transformation of *Brassica juncea* with the ECS gene from *E. coli* driven by double-enhanced 35S CaMV promoter, and wherein the analysis of heavy metal tolerance involves only hydroponic or agar medium with Cd concentrations of 0.15- 0.25 mM of CdSO₄ (page 8 of the specification, bottom paragraph;

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page 9, line 15 to page 10, line 11). The specification does not set forth obtention of other plant species overexpressing ECS for an enhanced accumulation. No guidance has been presented for the removal of exemplified or non-exemplified heavy metals from soil, ground or industrial waste water, or other heavy metal contaminated media by the exemplified or non-exemplified transgenic plants. The specification (pages 7-8, Table 2) discloses a number of plant species and the results for their transformation with an ECS gene for enhanced heavy metal accumulation from different media. However, it is unclear how these results were obtained, especially the “+++” for every transgenic species and “+/-” for every corresponding wild-type plant. Neither the actual values of the raw data, nor the statistical significance, were presented. It is also unclear how the “+++” corresponds to the “at least 50%” enhanced heavy metal accumulation from a wide variety of media.

In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Noctor et al teach unpredictability of the metabolism of plant glutathione synthesis and its response to heavy metal stress conditions (see, e.g., page 623, Abstract). For example, overexpression of ECS enzyme for phytochelatin (metal-binding compound) biosynthesis did

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NOT increase Cd tolerance in transgenic poplars grown in Cd contaminated soil (page 640, column 1, bottom paragraph). Furthermore, Applicants' own specification, page 3 lines 4-9, cites another reference as late as 1999 by Goldsbrough, who teaches that an overexpression of ECS gene did NOT increase the Cd tolerance of wild type *Arabidopsis thaliana* (see, e.g., page 230, last full paragraph). The publication date of Goldsbrough reference is after the priority date of the instant application, indicating the level of skill in the art even after the time of filing.

In addition, the prior art does NOT establish a definitive relationship between overexpression of ECS and enhanced accumulation of heavy metals. For example, de Knecht et al (1992) disclose Cd-tolerant *Silene vulgaris* plants synthesizing LESS phytochelatins than sensitive plants when exposed to the same concentration of Cadmium (see, e.g., page 681, Summary; page 685-687, Discussion). Chen et al teach that the observed cadmium tolerance in tomato cells which overproduce ECS was not stable over time, and that metal-tolerant plants exhibit inferior growth characteristics (page 238, column 1, first full paragraph). Also, Delhaize et al (1989) teach that relative overproduction of ECS or phytochelatins was not responsible for Cd tolerance in *Datura innoxia*. Hence, given the breadth of the claims; the unpredictability associated with the overexpression of ECS to induce heavy metal tolerance in transgenic plants or plant cells of a variety of species as evidenced by Noctor et al, Goldsbrough, de Knecht et al, Chen et al , and Delhaize et al; and lack of guidance as discussed above; the instant invention could not be practiced throughout the broad scope of the claims without undue trial and error experimentation .

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This Examiner's answer does not contain any new ground of rejection.

(11) *Response to Argument.*

Appellant should note that claims 1-24 are pending in this application, not claims 1-30 as stated on page 4 of the Brief of 25 January 2001.

(a) Enablement

Appellant insists , in pages 4-9 of the Brief of 25 January 2001, that the claims are patentable under 35 USC 112, first paragraph. Appellants rely upon the following arguments to support their position:

- assertions in the specification that a wide variety of plants may be used,
- putative results on pages 7-8 of the specification demonstrating enhanced heavy metal accumulation in a variety of divergent crop species,
- assertions in the specification that the claimed method is applicable to a variety of media such as soil or water,
- the limitation of the claims to recite a glutamylcysteine synthetase gene,
- the alleged reliance by Examiner upon "false allegations" and " a gratuitous legal citations" to support her arguments (page 6 of the Brief of 1/25/01),
- the Examiner's alleged confusion of non-obviousness with undue experimentation,
- the assertion by Appellants that " the prior art establishment of an uncertain and unpredictable relationship between glutamylcysteine synthetase expression and heavy metal exposure" should

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not be extrapolated to the instantly claimed methods or range of plant species (page 7 of the Brief, first full paragraph),

- the allegedly higher degree of experimentation and failure rate inherent in monoclonal antibody production which was not deemed “undue” in *Wands* , and
- the limitation of particular claims to particular plant species, heavy metals, or medium types.

These arguments are not persuasive because the claims are broader than the enabling disclosure.

Regarding the cited case law, the Examiner maintains that *Wands* is completely applicable to the instant application in its teachings of factors to be considered when making determinations of undue experimentation for enablement purposes. In particular, the *Wands* factors of claim breadth, lack of guidance, and unpredictability are extremely pertinent to the instant Appeal. Furthermore, the Examiner has correctly relied upon scientific literature, rather than “false allegations”, to support her position.

Regarding the issue of *unpredictability* as it relates to plant species, the Examiner has cited a variety of references which demonstrate that enhanced tolerance to cadmium or other heavy metals in a *variety* of non-*Brassica* plant species (as *broadly* claimed) was *not* associated with overexpression of glutamylcysteine synthetase (ECS), as instantly claimed. Specifically, overexpression of glutamylcysteine synthetase due to selection, spontaneous mutation, or other means, in tomato and *Datura* plants, did *not* result in stable or increased cadmium tolerance, as taught by Chen et al and Delhaize et al, respectively. In addition, *underexpression* of enzymes synthesizing phytochelatins (metal-chelating compounds) such as ECS in *Silene* plants resulted in

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cadmium tolerance, as taught by de Knecht et al. The failure of cadmium tolerance to be associated with ECS overexpression in three non-*Brassica* plant genera, coupled with Appellants' demonstration of ECS overexpression-mediated cadmium tolerance in only a single *Brassica* species, eminently supports the Examiner's position.

Furthermore, transgenic poplar plants which were transformed with the same *E. coli* ECS gene under the control of the same double CaMV 35S promoter as that utilized by Appellants (as taught by Arisi et al) failed to overaccumulate or tolerate cadmium, as taught by Noctor et al. In addition, transgenic wild-type *Arabidopsis* plants transformed with a tomato glutamylcysteine synthetase gene did not exhibit increased cadmium tolerance, as taught by Goldsbrough. Given the failure of these workers to obtain increased cadmium overaccumulation or tolerance in transformed non-*Brassica* plants, when transformed with the *same* gene encoding the *same* enzyme as that taught by Appellants and claimed in claim 1, and particularly when using the *same* gene source and *same* promoter as that taught by Appellants (Arisi et al as summarized by Noctor et al); the only reasonable explanation for Appellants' apparent success in a single *Brassica* species, namely *Brassica juncea*, is that the genetic background of the plant species to be transformed has a strong influence on the ability of the introduced transgene to cause heavy metal overaccumulation or tolerance.

Furthermore, Appellants have identified no special manipulation of the gene construct of Arisi et al which resulted in Appellants' success in contrast to Arisi et al's failure. In addition, no special transformation procedures or culture conditions were identified by Appellants which

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would explain their single instance of success, namely the ability of a single *Brassica* species, *Brassica juncea*, to overaccumulate cadmium when grown in a relatively non-complex hydroponic (aqueous) medium containing a known concentration of introduced cadmium salts. Thus, Appellants have provided a *lack of guidance* for the claimed obtention of heavy metal-tolerant and overaccumulating plants following transformation of a multitude of non-exemplified plant species with a gene encoding glutamylcysteine synthetase.

In addition, Appellants have provided a *lack of guidance* for the claimed method step of “identifying a medium as containing an excessive amount of a heavy metal” (see claim 13). No guidance is provided for obtaining or evaluating plants which allegedly accumulate heavy metals from structurally and biochemically complex media such as soil, which contains a multitude of microorganisms which interact in metabolizing, sequestering and/or secreting various metal ions; not to mention a multitude of structural components such as peat and clay which would bind metal ions to a stronger degree than would the simple aqueous solution taught in the specification. Furthermore, the soil microorganisms would alter the acidity of the soil due to their metabolic activity, which alteration would affect the soil’s ability to bind the heavy metal ions, which would affect the ability of plants to recover such ions from the soil and overaccumulate them. No guidance for any of these issues is provided in the instant specification.

Appellants’ putative results on pages 7 and 8 of the specification appear to be prophetic and are not interpretable as stated above, and fly in the face of the concrete data demonstrated by the five scientific publications cited above. Furthermore, Appellants’ mere *assertions* regarding

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the broad applicability of their claimed method to a variety of complex media or plant species are not sufficient to refute the *evidence* of unpredictability provided by the scientific publications and scientific reasoning provided by the Examiner. Similarly, Appellants' assertions, that the scientific publications cited by the Examiner should not be extrapolated to the instantly claimed methods or range of plant species, are of no moment and are not deemed probative.

In addition, Appellants' assertions that the Examiner has confused non-obviousness and undue experimentation are not persuasive. Although the references cited by the Examiner were originally submitted by Appellants to refute the Examiner's prior art rejection, those same references demonstrate the general lack of predictability in the claimed process, both at the time of filing and even later. This unpredictability, taken together with the claim breadth and lack of guidance as discussed above, clearly points to undue experimentation as established by *Wands*. Furthermore, Appellants' discussion on page 7 of the Brief, second full paragraph, through page 8, second full paragraph, seems equally drawn to prior art issues of non-obviousness ("fails to suggest" and "teaches away" on page 7, second full paragraph) *and* non-enablement ("unpredictable" on page 8, first and second full paragraphs, "unpredictability" on page 8, bottom paragraph).

Regarding Appellants' assertions that more experimentation would have been required to produce and evaluate monoclonal antibodies, which were deemed enabled by *Wands*, than the instantly claimed transformed plants and methods for their use, the Examiner disagrees. Although the production of monoclonal antibodies which react with a particular antigen might have a low

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success rate, the mechanisms by which said antibodies are produced and function is well-understood. The less than 3% success rate may be considered analogous to the rate of recovery of successfully transformed plants following transformation of a population of experimental plants or tissues with a particular gene of interest.

However, the unpredictability inherent in the instantly claimed process lies not within the method of transforming a plant with a particular gene to obtain a transformed plant, but with the *behavior and function* of that plant, and its *applicability in a method of its use for* heavy metal overaccumulation and tolerance. This very unpredictability was relied upon in the Examiner's withdrawal of the prior art rejections. Appellants argued that the poplar plants of Arisi et al which were transformed with the same gene as that employed by Appellants and which exhibited increased accumulation of the ECS protein encoded by the transgene, as expected, failed to *in fact* overaccumulate cadmium or be tolerant to high-cadmium growth media such as soil, as taught by Noctor et al, so that Arisi et al could not be relied upon to teach or suggest the claimed method of heavy metal overaccumulation and tolerance.

Regarding claim 3, Appellant insists, on page 10, top paragraph, that the claim is patentable under 35 USC 112, first paragraph, since it is limited to plants of the *Brassicaceae* family. This arguments is not persuasive because the claim is broader than the enabling disclosure. The specification provides guidance only for the transformation of *Brassica juncea* with an ECS gene from E.coli. The specification does not set forth obtention of other plant species from Brassicaceae such as *B. napus*, *B. campestris*, *B. oleraceae*, overexpressing ECS for

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an enhanced accumulation of the exemplified or non-exemplified heavy metals. The specification does not provide any evidence that an overexpression of ECS corresponds to enhanced heavy metal accumulation in any plant of the Brassicaceae family, including non-*Brassica* genera such as *Raphanus* or *Arabidopsis*. It is unpredictable whether said overexpression of ECS enzyme would induce enhanced heavy metal accumulation in said plants. For example, Goldbrough (see, e.g., page 230, last full paragraph) discloses that genes encoding gamma-glutamylcysteine synthetase (ECS) or GSH synthetase from tomato did not show any change in RNA expression in *Arabidopsis*, a Brassicaceae, exposed to Cd-stress condition. Therefore, the disclosure of a single plant species, namely *Brassica juncea*, does not provide an enablement for all plants of the Brassicaceae family.

Regarding claims 5- 7, and 14, Appellant contests that the claims are patentable under 35 USC 112, first paragraph as the particularly recited elements are specifically exemplified as shown in Table 2 of the specification. This argument is not persuasive because the claims are broader than the enabling disclosure, with regard to plant species as discussed above.

Regarding claim 19, Appellant contests, on page 10, that the claim drawn to soil medium is patentable under 35 USC 112, first paragraph as Table 2 of the specification (page 7) exemplified various suitable soil media. This arguments is not persuasive because of the putative nature of the results of Table 2 and the lack of actual guidance regarding evaluation of metal accumulation by plants grown in any soil type, as stated above.

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CONCLUSION

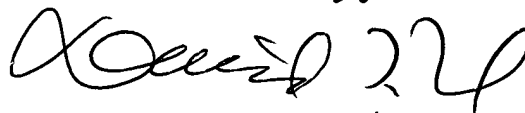
For the reasons discussed above, it is believed that claims 1-3, 5-8, 13-15, 22 are not in compliance with 35 USC 112, first paragraph. Hence, the rejection should be maintained.


Respectfully Submitted,

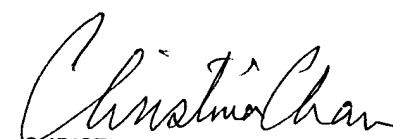
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